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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

(57) Abstract

The present invention relates to a composition containing novel proteins and methods for the diagnosis and treatment of immune related diseases.

surface of an antigen presenting cell and CD28 and CTLA-4 molecules expressed on the T cell surface effect T cell activation. Activated T cells express an increased number of cellular adhesion molecules, such as ICAM-1, integrins, VLA-4, LFA-1, CD56, *etc.*

T-cell proliferation in a mixed lymphocyte culture or mixed lymphocyte reaction (MLR) is an established indication of the ability of a compound to stimulate the immune system. In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Immune related diseases can be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

## Summary of the Invention

The present invention concerns compositions and methods for the diagnosis and treatment of immune related disease in mammals, including humans. The present invention is based on the identification of proteins (including agonist and antagonist antibodies) which either stimulate or inhibit the immune response in mammals. Immune related diseases can be treated by suppressing or enhancing the immune response. Molecules that enhance the immune response stimulate or potentiate the immune response to an antigen. Molecules which stimulate the immune response can be used therapeutically where enhancement of the immune response would be beneficial. Such stimulatory molecules can also be inhibited where suppression of the immune response would be of value.

Neutralizing antibodies are examples of molecules that inhibit molecules having immune stimulatory activity and which would be beneficial in the treatment of immune related and inflammatory diseases. Molecules which inhibit the immune response can also be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

Accordingly, the PRO polypeptides and anti-PRO antibodies and fragments thereof are useful for the diagnosis and/or treatment (including prevention) of immune related diseases. Antibodies which bind to stimulatory proteins are useful to suppress the immune system and the immune response. Antibodies which bind to inhibitory proteins are useful to stimulate the immune system and the immune response. The PRO polypeptides and anti-PRO antibodies also useful to prepare medicines and medicaments for the treatment of immune related and inflammatory diseases.

In one embodiment, the invention provides for isolated nucleic acid molecules comprising nucleotide sequences that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about

Figure 126 shows the native sequence PRO4430 polypeptide UNQ1947 (SEQ ID NO:295).

Figure 127 shows DNA98853-1739 (SEQ ID NO:296).

Figure 128 shows the native sequence PRO5727 polypeptide UNQ2448 (SEQ ID NO:297).

## Detailed Description of the Preferred Embodiments

### I. Definitions

The terms "PRO polypeptide(s)" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (*i.e.*, "PRO/number" or more particularly, PRO200, PRO204, PRO212, PRO216, PRO226, PRO240, PRO235, PRO245, PRO172, PRO273, PRO272, PRO332, PRO526, PRO701, PRO361, PRO362, PRO363, PRO364, PRO356, PRO531, PRO533, PRO1083, PRO865, PRO770, PRO769, PRO788, PRO1114, PRO1007, PRO1184, PRO1031, PRO1346, PRO1155, PRO1250, PRO1312, PRO1192, PRO1246, PRO1283, PRO1195, PRO1343, PRO1418, PRO1387, PRO1410, PRO1917, PRO1868, PRO205, PRO21, PRO269, PRO344, PRO333, PRO381, PRO720, PRO866, PRO840, PRO982, PRO836, PRO1159, PRO1358, PRO1325, PRO1338, PRO1434, PRO4333, PRO4302, PRO4430 or PRO5727) refers to particular polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation (*e.g.*, as described above) as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

A "native sequence PRO polypeptide(s)" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO/number polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide(s)" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO/number polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO/number polypeptides disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The "PRO polypeptide(s) extracellular domain" or "ECD" refers to a form of the said polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein.

Figure 128

MDCQENEYWDQWGRCVTCQRCGPGQELSKDCGYGEGGDAYCTACPPRRYKSWGHHRCQ
SCITCAVINRVQKVNCTATSNAVCGDCLPRFYRKTRIGGLQDQECIPCTKQTPTSEVQC
AFQLSLVEADAPTVPPQEATLVALVSSLLVVFTLAFLGLFFLYCKQFFNRHCQRVTGGL
LQFEADKTAKEESLFPVPPSKETSAESQVSENIFQTQPLNPILEDDCSSTSGFPTQESF
TMASCTSESHSHWVHSPIECTELDLQKFSSSASYTGAETLGGNTVESTGDRLELNVPFE
VPSF